EANO guidelines for the diagnosis and treatment of meningiomas

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Abstract: Although meningiomas are the most common intracranial tumours, the level of evidence to provide recommendations for the diagnosis and treatment of meningiomas is low compared with other tumours such as high-grade gliomas. The meningioma task force of the European Association of Neuro-Oncology (EANO) assessed the scientific literature and composed a framework of the best possible evidence-based recommendations for health professionals. The provisional diagnosis of meningioma is mainly made by MRI. Definitive diagnosis, including histological classification, grading, and molecular profiling, requires a surgical procedure to obtain tumour tissue. Therefore, in many elderly patients, observation is the best therapeutic option. If therapy is deemed necessary, the standard treatment is gross total surgical resection including the involved dura. As an alternative, radiosurgery can be done for small tumours, or fractionated radiotherapy in large or previously treated tumours. Treatment concepts combining surgery and radiosurgery or fractionated radiotherapy, which enable treatment of the complete tumour volume with low morbidity, are being developed. Pharmacotherapy for meningiomas has remained largely experimental. However, antiangiogenic drugs, peptide receptor radionuclide therapy, and targeted agents are promising candidates for future pharmacological approaches to treat refractory meningiomas across all WHO grades.

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EANO Guidelines for the Diagnosis and Treatment of Meningiomas

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Abstract

This guideline provides background information and practical recommendations for the diagnosis and treatment of patients with intracranial and spinal meningiomas. Although meningiomas represent the most common intracranial tumors, the level of evidence for recommendations that can be derived from the literature is low compared to other tumors. The meningioma task force of the European Association for Neuro-Oncology (EANO) assessed the literature available and composed a framework of best possible evidence-based recommendations for health professionals. The provisional diagnosis of meningioma is mainly made by magnetic resonance imaging. Definitive diagnosis including histological classification, grading, and molecular profiling requires a surgical procedure to obtain tumor tissue. In many elderly patients, observation is the best therapeutic option. If therapy is deemed necessary, standard treatment is gross total surgical resection including the involved dura. As an alternative, radiosurgery can be performed for small tumors or fractionated radiotherapy in large or previously treated tumors. Treatment concepts combining surgery and radiosurgery or fractionated radiotherapy are evolving allowing treatment of the complete tumor volume with low morbidity. Pharmacotherapy for meningiomas has remained largely experimental. However, anti-angiogenic drugs, peptide receptor radionuclide therapy and increasingly targeted agents are promising candidates for future pharmacological approaches to refractory meningiomas across all WHO grades.

Keywords: meningioma, atypical ~~meningioma~~, anaplastic ~~meningioma~~, outcome, surgery, radiosurgery, radiotherapy, observation, embolization

Introduction

Meningiomas are the most common primary intracranial tumors. Most meningiomas are WHO grade I lesions whereas a minority are classified as WHO grade II or even grade III lesions, based on local invasiveness and cellular features of atypia[1]. The vast majority of patients can be cured by surgery alone, notably patients with WHO grade I tumors at favorable locations. Beyond surgery, various approaches of radiotherapy are commonly used to increase local control, particularly if surgery alone seems not to be sufficient. In contrast, pharmacotherapy has so far assumed only a minor role in the management of meningiomas. Although management may appear to be fairly standardized across the globe, there are very few controlled clinical trials, resulting in a situation where standards of care are defined by local experience, long-standing traditional procedures, and experience-based practice. However, there are numerous situations where more than one approach appears feasible. For example, is there a need for intervention in case of incidental meningiomas of unclear growth kinetics? Furthermore, do all meningioma-suspect lesions require histological verification of the diagnosis? When is the right time and what is the right fractionation approach when radiotherapy is considered? How will medical therapy

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develop in the future and what is the role of molecular profiling? Defining standards of care and outlining answers to some of these difficult questions is the purpose of the present guideline prepared by a task force of EANO.

Methods

The authors searched the following databases: the Cochrane Library from January 1990 until May 2016~~to date~~, the Medline databases from January 1990 to May 2016~~date~~, Embase-Ovid (January 1990 to May 2016~~date~~), Cancer Net, Science Citation Index. Sensitive and specific keywords as well as combinations of keywords were used. Only publications in English were considered. ~~Publications in any language of the countries represented by this EANO task force were considered.~~ Search started May 1st 2015 and finished May 16th 2016. The main keywords were meningioma, atypical ~~meningioma~~, anaplastic ~~meningioma~~, outcome, surgery, radiosurgery, radiotherapy, chemotherapy, observation, embolization, ~~Simpson~~ in various combinations.

The literature available was evaluated and the scientific evidence was sorted into classes I-IV and recommendations were rated at level A-C, according to EFNS guidelines[2]. When sufficient evidence for recommendations was not available, the task force offered advice as "good practice point".

General recommendations

Recommendations for the diagnostic and therapeutic management of meningioma patients in general, including epidemiology and clinical presentation, pathogenesis and risk factors, diagnostic procedures, therapeutic decision making, surgical and radiotherapeutic approaches as well as pharmacotherapy are summarized in the appendix. WHO grading is displayed in table 1[3].

Specific recommendations

Recommendations for therapeutic management of meningiomas of WHO grades I-III are outlined in figure 1.

Meningioma WHO grade I

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Meningiomas can be diagnosed by magnetic resonance imaging (MRI) and additional computed tomography (CT) in most cases with high probability (figure 2)[4]. They usually present as solitary round tumors, with close contact to the dura mater and strong enhancement after contrast injection. The typical appearance of meningioma is isointense on T1 weighted imaging, iso- or hyperintense on FLAIR and with high and homogenous enhancement following gadolinium injection. ~~On T2 weighted imaging, the meningeal arteries can sometimes be seen as lines of low signal radiating from the center of the tumor (typical "sunburst" appearance).~~ Thickening of the dura mater at the perimeter of the tumor (so-called dural tail) is displayed by T1 with gadolinium[5]. CT is valuable for the detection of calcification within the tumor, hyperostosis of adjacent bone and intraosseous tumor growth, particularly in skull base meningiomas. Conventional cerebral angiography ~~is no longer used for~~has no routine role in the diagnosis of meningioma, but can be used as an adjunct to treatment planning in selected cases~~It is only used for therapy planning in selected cases~~. Delineation of complex skull base meningiomas may be challenging. The expression of somatostatin receptor 2 of meningiomas can be used for discrimination from healthy tissue by using peptide ligands such as (68)Ga-Dotatate or (90)Y-Dotatoc as PET tracers[6,7]. Therefore, an improvement of diagnostic management of complex meningiomas can be expected in the near future.

Beyond neurofibromatosis type 2 (NF-2), several genes have been detected as frequently mutated in these tumors - for example KLF4 and TRAF7 are often~~always~~ mutated in secretory meningioma[8]. It is of interest that mutations in these genes are not randomly distributed in meningiomas but form groups with typical combinations of mutations and exclusion of other mutations. It is expected that a molecularly based classification will be developed and that this classification has the potential to direct individualized meningioma-specific therapy (tables 2 and 3). ~~More relevant, p~~Preliminary findings point to TERT mutations, irrespective of WHO grade, being an indicator for more aggressive growth in meningioma[9,10]. Molecular alterations associated with less favorable clinical courses are expected to develop as valuable adjuncts to tumor grading for identifying patients at higher risk for meningioma recurrence or progression. Additional work to correlate molecular signatures with risk of tumor recurrence and prognosis is needed. On the other hand, molecular screening should be able to offer ~~to more reliably select and predict which patients will benefit from adjuvant~~targeted therapy for a subset of patients.

Therapy of meningioma patients needs to be individualized due to the different nature of meningiomas and the potential consequences of different treatments to the patients. Many~~ost~~ asymptomatic, incidentally discovered meningiomas can be managed by observation using annual clinical and MRI intervals, after an initial observation interval of 6 months[11]. There is no class I or II evidence to support guidelines for observational management of meningiomas, but there are numerous retrospective series and several reviews validating this concept[12] (evidence level III, recommendation level C). The suggestion to treat with surgery rather than observation should be based on a solid indication. Although surgery is for the majority of patients the only treatment needed, its long-term sequelae are often

overlooked; in a recent study it was shown that forty percent of the patients operated for a meningioma experienced cognitive or emotional problems following surgery[13]. If imaging is highly suggestive of meningioma, histological verification is not mandatory; however, it is recommended to exclude rare differential diagnoses like metastasis (recommendation level: good practice point). The diagnostic and therapeutic role of molecular profiling, which makes the availability of tumor tissue necessary, still needs to be established. If therapy is needed because of radiologically confirmed growth or presence of clinical symptoms, surgery is the therapy of first choice (evidence level II, recommendation level B). The aim of microsurgery is complete tumor removal (gross total resection, GTR) including involved dura corresponding to Simpson grade I resection. Extent of resection (EOR) is defined by the Simpson Grade (table 4) that relies on the surgeon's assessment at surgery and is an important prognostic factor for risk of tumor recurrence[14]. Even if the Simpson classification pre-dates modern neuro-imaging and several authors see a limited value, it still proved to be valuable for assessing the risk of recurrence in recent series[12,15]. Today, the intraoperative assessment of EOR should be confirmed by postoperative MRI that can be performed within 48 h after surgery or after 3 months to avoid artifacts. Preoperative embolisation is not generally recommended, however, it may facilitate surgery in selected cases (evidence level IV, recommendation level C).

As an alternative to surgery in elderly patients, for tumors not safely accessible by surgery, or after incomplete surgical resection, stereotactic radiosurgery (SRS) can be offered for~~in case of~~ small tumors. A series of 35 retrospective studies showed a 5 year PFS of 86-100 percent after primary SRS[16]. If the tumor volume cannot be treated by a single fraction, fractionated radiotherapy (RT) with 50-55 Gy given in 1·8-2.0 Gy per fraction can be applied (evidence level III, recommendation level B). After RT, control rates of 75 to 92 %~~ percent~~ are described in various series[17-21]. When RT is added to subtotal resection (STR), control rates and survival similar to GTR are reported[22,23]. In order to spare tumor-surrounding sensitive neurovascular structures and to diminish the~~ well known~~ risk of long term cognitive deterioration, intensity modulated radiation therapy (IMRT) and fractionated stereotactic radiotherapy (FSRT) are increasingly used, offering similar control rates with conventional RT[24-26]. In selected cases of small meningiomas, SRS allows a single application of 14-16 Gy[27-32]. The use of planned combination therapies consisting of STR or partial resection followed by SRS or RT allows treating the complete tumor whereas reducing the risk of treatment[30] (evidence level IV, recommendation level C). After therapy, annual MRI controls for 5 years are sufficient, followed by bi-annual controls. There are no strong data supporting the use of pharmacotherapy in meningiomas of WHO grade I[33-36], but this may change soon with the recent identification of druggable mutations (see table 3~~ below~~)[37]~~.~~ Peptide receptor radionuclide therapy (PRRT) has shown some effect in small series and will be evaluated in clinical studies[38-42]. Key recommendations regarding therapy are summarized in Table ~~1~~5.

Meningioma WHO grade II

There are no clear radiological criteria to distinguish WHO grade I and grade II meningiomas. Exposure to ionizing radiation has been firmly linked to a higher risk for meningiomas and radiation-associated meningiomas are more likely to be atypical or malignant and multifocal[43-47]. ~~The presence of type 2 neurofibromatosis (NF2) implies a risk of developing malignant or multiple meningiomas, whereas the role of NF2 in developing grade II or III meningiomas is not clear.~~ ~~There are increasing d~~Data allowing ~~the~~for a molecular genetic characterization of atypic and malignant meningiomas accumulate, e.g.. TERT mutations are associated with higher meningioma grades[9,48].

Surgery is the first choice of treatment and should aim at a Simpson I resection (evidence level III, recommendation level B). The diagnosis of WHO grade II meningioma implies an increased risk of recurrence requiring shorter control intervals (6 months instead of annual, see below)[49]. The role of RT as an adjuvant therapy is still open. Retrospective series on adjuvant RT after GTR led to differing results and prospective data on adjuvant RT after GTR are missing[50-56]. The ROAM / EORTC 1308 trial (ISRCTN71502099) is currently recruiting patients with newly diagnosed atypical meningioma (WHO grade II) who have undergone gross total resection (Simpson I-III) and will be randomized between early adjuvant radiotherapy (60 Gy in 30 fractions) and observation to determine whether RT~~radiotherapy~~ reduces the risk of or delays tumor recurrence[57]. For incompletely resected tumors, adjuvant RT (54 to 60 Gy given in 1·8-2·0 Gy per fraction) should be considered (evidence level III, recommendation level C). In cases of progression, RT should be performed if not done following the initial surgery, with or without second surgery (evidence level III, recommendation level C). If the diagnosis of a WHO grade II or III is made, fractionated radiotherapy is preferred to S~~tereotactic radiosurgery~~RS techniques, although SRS offers similar results for small tumors or tumor remnants[58-60]. There are no data about PRRT in meningioma WHO grade II. In any case, due to lack of definite data regarding adjuvant RT~~radiotherapy~~ and considering the potential long-term effects of RT, discussion with the patient prior to any decision is mandatory. The patients should be informed about potential long-term toxicity, which can occur in up to 53% of cases after RT and a mean follow-up of 12 years[23,61]. Retrospective studies and small prospective studies have evaluated a range of drugs including hydroxyurea, cycophosphamide/adriamycin/vincristine chemotherapy, interferon-alpha, megestrol acetate, medroxy-progesterone acetate, octreotide, sandostatin LAR, pasireotide LAR, imatinib, erlotinib, gefitinib, vatalanib, sunitinib and bevacizumab in WHO grade II and III meningiomas[33]. PFS-6 rates ranged from 0% to 64% and median OS times from 6 to 33 months in patients progressing after surgical resection and radiotherapy. The most promising results have been reported for bevacizumab, vatalanib and sunitinib, all drugs with anti-angiogenic properties[33,62-66]. These results need to be confirmed in prospective controlled trials, before clinical use of these compounds in WHO grade II and III meningiomas can be recommended. An ongoing EORTC phase II trial (NCT02234050) explores the efficacy of trabectedin, a tetrahydroisoquinoline that has shown promising activity in recurrent WHO grade II and grade III meningiomas[67]. Altogether,

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pharmacotherapy ~~can~~should be considered upon further progression in meningiomas WHO grade II (evidence level IV, recommendation level C).

Meningioma WHO grade III

Anaplastic meningiomas often are more irregularly shaped and display a higher relative cerebral blood volume than~~compared to~~ WHO grade I and II tumors[4]. They ~~Meningiomas WHO grade III~~ have a strong tendency to recur and may metastasize systemically. There is a high proportion of NF2 mutations in WHO grade III meningiomas (table ~~2~~3), diffuse growth and invasion of the cortex is often described[68]. Surgical resection should be as radical as possible (evidence level III, recommendation level C) and needs to be followed by fractionated radiotherapy with at least 54 Gy in 1.8-2 Gy fractions (evidence level III, recommendation level B). Current clinical trials address the question of dose: In the RTOG 0539 trial, WHO grade II meningiomas are treated by RT with 54 Gy in 30 fractions after GTR, while "high risk meningioma" (i.e. WHO grade II recurrent disease, WHO grade II after STR resection and all WHO grade III) receive up to 60 Gy (NCT00895622). In the EORTC 22042-26042 trial (NCT00626730), WHO grade II and grade III tumors post GTR wea~~a~~re irradiated with 60 Gy in 30 fractions. After STR, 60 Gy plus a 10 Gy boost on the remaining tumor volume wea~~a~~re delivered. Results are pending. Follow-up should be performed three months after initial therapy, then every 3 or 6 months, depending on initial growth kinetics. Pharmacotherapy options remain experimental (evidence level IV, recommendation level C) and only little data on the efficacy of antineoplastic drugs in WHO grade III meningiomas are available. No clinical trials have focussed on WHO grade III tumors, but small numbers of these neoplasms have been included in most studies together with WHO grade II tumors (see above). Consequently, no specific recommendations can be made for pharmacotherapy of WHO grade III meningiomas ~~and patients with this diagnosis should be enrolled into clinical trials whenever possible~~.

Spinal meningiomas

Surgical resection to remove the tumor and decompress the spinal cord is the therapy of choice for patients with~~in~~ spinal meningiomas. The majority of data supports surgical strategies striving for completeness of excision. Recurrence rates of spinal meningiomas after surgical resection have been reported in the range of 1·3 – 14·7%[69-72]. There is consensus that incomplete resection is a risk factor for recurrence but it is unclear whether Simpson grade I resection achieves better long term outcome than Simpson grade II resection[69,72-74]. Most papers report lower recurrence rates after resection of the involved dura but at the cost of a higher complication rate, particularly for meningiomas located unfavorably or with severe calcification[71]. Therefore, Simpson grade I resection should be aimed for in all

cases of spinal meningioma with a favorable location, but only if this can be achieved without compromising neurological function and if a safe and uncomplicated dural repair is feasible (recommendation level: good practice point). For patients with ventrally located meningiomas or with calcified dural attachment, excision of the dura should not be the goal – coagulation of the dural attachment is sufficient. For the rare cases where (i) surgical resection cannot be performed for any reason, (ii) stopping tumor growth is the only aim of treatment and (iii) decompression of the spinal cord does not seem necessary, SRS or hypofractionated radiotherapy is an alternative to surgical resection[75] (recommendation level: good practice point). Adjuvant therapy is performed according to the WHO grade and resection status as stated above for cranial meningiomas.

Surveillance and follow-up

Follow-up is needed to prevent future potentially irreversible neurological deficits and to find the optimal timing for potential (re-)intervention. There is no robust data on the best follow-up schedule for meningiomas, since most retrospective studies do not report on monitoring intervals and since prospective studies published so far had variable follow-up protocols, usually tailored to fit the treatment visits[76,77]. Therefore, the following recommendations are based more on expert consensus opinion rather than evidence (recommendation level: good practice point).

Follow-up should be performed clinically by an experienced neurosurgeon or neurooncologist and must be accompanied in special cases by additional specialists, e.g., if cranial nerve function is threatened. There is considerable variation in follow-up intervals possible depending not only from resection status, size and location of the tumor, but also age and the general and neurological status of the patient.

Our proposed approach for ~~rn~~ the management of small, asymptomatic meningiomas is to evaluate the dynamics of the tumor with MRI with contrast medium 6 months after initial diagnosis and then annually, as long as the patient remains asymptomatic. After five years this interval can be doubled. In patients with limited life expectancy due to high age or severe co-morbidities, controls may be omitted if the radiological diagnosis of a benign meningioma seems clear.

Monitoring after initial treatment depends on the EOR and grading of the tumor.

For WHO I meningiomas resected totally (GTR), the 10-year recurrence rates vary from 20-39%. ~~Studies with long follow-up with MRI show that recurrence is more common than previously thought~~[17,22,78]. Therefore, it is advisable to perform a baseline MRI within 48 hours or after 3 months, in order to assess the EOR. Thereafter, we propose annual MRI controls until five years post treatment, then every two years.

If resection is known to be incomplete, EOR should be documented by early postoperative MRI within 48 hours. For WHO grade I tumors after STR, the 10-year progression rates vary between 55 and 100% suggesting a more vigilant long-term follow-up[78,79]. For those cases, MRI at 6 and 12 months is recommended, then annually.

The natural history of WHO grade II meningiomas is less clear~~, since the 2007 WHO criteria changed their definition and thus their identification rates~~. The 5-year recurrence/progression rates may be as high as 30% and 40% after GTR and STR, respectively[50,51]. In these tumors, we suggest an early postoperative MRI within 48 hours. Follow up MRI should be done every 6 months for 5 years, then annually.

For WHO grade III meningiomas ~~are aggressive tumors with very poor local control, even after multimodal treatment. In the recent studies utilizing the WHO 2007 grading scheme,~~ the 5-year-PFS ranged from 12 to 57%, even after resection and radiotherapy. Therefore, these tumors have to be followed up very closely[80]. After the initial, early post-treatment MRI, cranial imaging should be routinely done every 6 months, in rapidly growing cases every 3 months. Key recommendations for follow-up are summarized in table ~~15~~.

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Supportive care and patient management

Most meningiomas are diagnosed in asymptomatic patients[11] ~~(Zitat 10).~~ Patients with larger tumors may suffer from epilepsy, focal neurologic deficits, vascular complicatons, notably deep venous thrombosis and pulmonary embolism, chronically raised intracranial pressure and neurocognitive impairment (Zitate 7-11 from appendix). Acute and long term treatment of these aspects of meningiomas ~~problems and management of the patients affected is~~ are similar to the ~~treatment and~~ management of patients with other intracranial tumors such as gliomas[81-83]~~. Guidelines for supportive care for these patients have been described elsewhere (Soffietti, LGG 2010, Weller HGG, 2014).~~.

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Weller M, Stupp R, Wick W. Epilepsy meets cancer: when, why, and what to do about it? Lancet Oncol 2012;13:e375-e382

Kommentiert [RG5]: Wie gehabt

Future directions

There is promising progress ~~i~~on several areas ~~fields in~~of the diagnosis and therapy of meningiomas. The new WHO classification of tumors of the nervous system has refined the subclassification by morphology and grade for meningiomas, and recent high-throughput studies have defined novel driver mutations that are potentially druggable in subsets of tumors. ~~A major challenge is comprehensive molecular genetic characterization of meningiomas of all grades. Genetic profiling will allow for individual estimation of prognosis and offer personalized, targeted therapies.~~ Diagnosing the extension of complex meningiomas, e.g. pretreated intraosseous skull base tumors, still is challenging. ~~As stated above,~~ PET ~~imaging~~ using tracers binding to somatostatin receptor 2 like (68)Ga-Dotatate or (90)Y-Dotatoc is a promising technique

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Das war chirurgisch gedacht. So ist es hoffentlich klarer.

that will have an increasing role for delineation of these tumors and therapy planning. This imaging technique may also find a place in the ~~could (will?) also influence~~ RANO ~~(response assessment in neuro-oncology)~~ criteria for meningiomas that are currently under development[16]~~d (Zitat Leland Rogers, 2015)~~. Surgical techniques and approaches are more and more refined in terms of individualized risk assessment. In case of skull base meningiomas, therapeutic concepts combining subtotal resection and radiosurgery will be used more often in order to minimize ~~the~~ treatment risk ~~for the patient~~. Multi~~Inter~~disciplinary diagnosis and therapy of meningiomas planned in dedicated ~~is an issue that will be increasingly discussed in~~ brain tumor boards should become standard of care. An increasing number of prospective studies ~~assessing~~ efficacy and safety of ~~established and~~ novel systemic therapies are on their way. These will help to generate higher levels of evidence for future~~meningioma~~ treatment concepts and hopefully better outcomes for the minority of tumors that are still difficult to control.

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Conclusions

The ~~general~~ levels of evidence for diagnosis and treatment recommendations for patients with ~~of~~ meningiomas are low, allowing only recommendations of level B, C and good practice points, despite the relative frequency of such tumors. ~~However, there are n~~Numerous efforts to generate new evidence by prospective studies pointing at this currently unmet need in neurooncology are ongoing. The key recommendations of the EANO task force which represent the state of knowledge of June 2016, are outlined in table ~~1~~5.

Contributors

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All authors contributed in the preparation of the manuscript and literature search. All authors reviewed the paper and approved the final version. EH provided figures. RG and MW developed the concept for the guidelines. RG composed the final draft.

Declaration of interests

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RG has received honoraria for advisory boards from MagForce, Bristol-Myers-Squibb and Roche. MJ is the CI of the ROAM trial investigating radiation versus observation following surgical resection in atypical meningioma and has received research grant from the NIHR-HTA. MP has received research grants from Böhringer-Ingelheim, GlaxoSmithKline, MSD and Roche and honoraria from Bristol-Myers Squibb, Novartis, Gerson Lehrman Group and CMC Contrast. MW has received research grants from Acceleron, Actelion, Isama, MSD, Merck Serono EMD, Novocure, Piqur and Roche and honoraria from Isama, MSD,

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Tables

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Table 1: 2016 WHO grading for meningiomas [1]

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WHO Grade	Description
Grade I	Low mitotic rate (less than 4 per 10 high power fields (HPF) Absence of brain invasion 9 subtypes
Grade II (atypical)	Mitotic rate: 4-19 per HPF, *or* brain invasion *or* 3 out of 5 specific histologies: spontaneous necrosis, sheeting, prominent nucleoli, high cellularity, small cells~~clear cell or chordoid cell types~~
Grade III (anaplastic)	Mitotic rate: >20 per HPF *or* specific histologies: Papillary or rhabdoid meningioma

Table 2: Mutations in meningiomas [27,28,30]

	AKT1	KLF4	TRAF7	NF2	SMO	TERT
Meningothelial Meningioma WHO grade I	13%	-	8%	22%	16%	-
Transitional Meningioma WHO grade I	14%	-	5%	33%	-	-
Fibroblastic Meningioma WHO grade I	-	-	-	70%	-	-
Psammomatous M. WHO grade I Meningioma WHO grade I	-	-	-	60%	-	-
Secretory Meningioma WHO grade I	-	100%	100%	-	-	-
Lymphoplasmacyte-rich Meningioma WHO grade I	no data	no data	no data	no data	no data	no data
Metaplastic Meningioma WHO grade I	25%	-	-	20%	-	-
Microcystic Meningioma WHO grade I	-	-	-	-	-	-
Angiomatous Meningioma WHO grade I	4%	-	-	10%	-	-
Atypical Meningioma WHO grade II	4%	-	4%	70%	-	6%
Chordoid Meningioma WHO grade II	-	-	-	-	-	-
Clear Cell Meningioma WHO grade II	-	-	-	50%	-	-
Anaplastic Meningioma WHO grade III	-	-	-	70%	-	20%
Rhabdoid Meningioma WHO grade III	no data	no data	no data	no data	no data	no data
Papillary Meningioma WHO grade III	no data	no data	no data	no data	no data	no data

Percentages, values <4% are given as "-"

Table 3: Possible targets for future therapies

Potential drug / drug class	**Molecular target / biomarker**
AKT inhibitor	AKT1 (p.Glu17Lys) mutation[84,85] ~~27,28~~
Hedgehog inhibitor	SMO (p.Trp535Leu) mutation ~~27,28~~10,84
FAK inhibitor	NF2/merlin loss[86,87] ~~115,116~~
Immune checkpoint inhibitor	PD1-/PD-L1[88] ~~117~~
VEGF or VEGFR inhibitor	VEGF/VEGFR2[63,89,90] ~~105,118,119~~
PI3K inhibitors	PI3K[91]
Trabectedin	DNA, tumor-associated macrophages, angiogenesis ~~109~~67

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Kommentiert [RG10]: Die Referenzen stimmen nicht!!!

Kommentiert [RG11]: Idem

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Kommentiert [WM13]: Oncogenic PI3K mutations are as common as AKT1 and SMO mutations in meningioma
Malak Abedalthagafi†, Wenya Linda Bi†, Ayal A. Aizer†, Parker H. Merrill†, Ryan Brewster, Pankaj K. Agarwalla, Marc L. Listewnik, Dora Dias-Santagata, Aaron R. Thorner, Paul Van Hummelen, Priscilla K. Brastianos, David A. Reardon, Patrick Y. Wen, Ossama Al-Mefty, Shakti H. Ramkissoon, Rebecca D. Folkerth, Keith L. Ligon, Azra H. Ligon, Brian M. Alexander‡, Ian F. Dunn‡, Rameen Beroukhim‡, and Sandro Santagata‡

NEURO-ONCOLOGY in press

Table 4: Simpson grades of resection and corresponding EORTC/RTOG definitions of extend of resection

Grade	Definition	Extent of Resection (EOR)
I	Gross total resection of tumor, dural attachment and abnormal bone	GTR
II	Gross total resection of tumor, coagulation of dural attachment	GTR
III	Gross total resection of tumor without resection or coagulation of dural attchments, or extradural extensions (e.g. invaded or hyperostotic bone)	GTR
IV	Partial resection of tumor	STR
V	Biopsy of tumor	

Table 5: Key recommendations for the management of meningiomas.

Diagnosis
The radiological diagnosis of meningioma should be made by MRI
Conventional angiography should be restricted to selected cases
Tissue for future molecular analysis should be stored if available
Histological verification of meningioma is not mandatory in all cases
Treatment
Asymptomatic patients may be managed by observation
If treatment is indicated in meningioma of any WHO grade, surgery is the first option
Complete removal (Simpson I) is the primary goal of surgery
The degree of resection should be confirmed by MRI
Embolisation should be restricted to selected cases
Radiosurgery may be the first option in small WHO grade I meningiomas in specific locations

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~~Radiosurgery may be the first option in small WHO grade I meningiomas in specific locations~~
Patients with meningioma WHO grade I that cannot be operated on can be treated by fractionated radiotherapy or radiosurgery
Combining subtotal resection and radiosurgery or fractionated radiotherapy should be considered to allow comprehensive tumor treatment while reducing the risk of adverse effects from treatment in WHO grade I meningiomas
Patients with incompletely resected meningiomas WHO grade II should receive fractionated radiotherapy
Pharmacotherapy is experimental in any grade of meningioma and should only be considered if no further surgical or radiotherapy options exist
Follow-up ~~annually~~yearly
Follow-up of patients with WHO grade I meningiomas should be done yearly, after 5 years biannually
Follow-up of WHO grade II meningiomas should be done every 6 months, after 5 years yearly
Follow-up of WHO grade III meningiomas should be done every three to six months

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Figure Legends:

Figure 1:

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Recommendations for therapeutic management of meningiomas of WHO grades I-III

Figure 2

Meningioma of the right convexity with typical radiological signs
A : Bone window of the cerebral CT scan in coronal view showing hyperostosis facing the tumor
B: Cerebral MRI (FLAIR) showing the tumor slightly hyperintense. Note the edema of the parenchyma adjacent to the tumor (arrow)
C: T2 sequences in coronal view showing CSF (small arrows) interposed between tumor and parenchyma demonstrating the extra-axial nature of the tumor
D : T1 weighted MRI after gadolinium injection depicting intense enhancement of the tumor. Note the large contact of the tumor with the dura-mater and the thickening of the adjacent dura-mater (arrow).

Appendix:

Epidemiology and clinical presentation

Meningiomas have the highest incidence rate among all intracranial and intraspinal tumors. In European countries the annual incidence rate of meningiomas is 4·2 per 100·000 individuals[1,2]. The median age at diagnosis is 65 years and incidence increases with age[3]. The majority of intracranial meningiomas are found in the supratentorial compartment, most commonly at the cerebral convexity, along the dural venous sinuses, along the falx or intraventricularly. Skull base meningiomas grow at the sphenoid wing, olfactory groove, clinoid process or petroclival regions. Additional sites include the cerebellopontine angle, the foramen magnum or – less commonly – the optic nerve sheath. Moreover, meningiomas represent 25-45% of intradural spinal tumors[4]. Eighty percent of spinal meningiomas are located in the thoracic spine[5]. Many meningiomas are asymptomatic and diagnosed incidentally. There is no clearly defined critical size for the development of symptoms in general, however, meningiomas ~~that the general rule is that meningiomas~~ that do not exceed 2.5 cm in diameter~~,~~ rarely cause symptoms within 5 years of being discovered[6]. An exception can be smaller meningiomas, growing close to critical structures (such as the optic nerve) or meningiomas with disproportionally large edema or rate of growth. The most common symptoms are epilepsy, or headache for weeks to months, or location-specific symptoms or signs such as unilateral weakness, visual field loss, changes in personality or speech problems. Meningioma patients exhibit~~have~~ diminished neurocognitive function as compared with healthy controls except for intelligence and visuoconstructive skills[7-11]. Neurocognitive functions in patients with meningiomas in the dominant hemisphere (usually left-side) are more compromised than in patients with meningiomas in the non-dominant hemisphere (usually right-side). Furthermore, neuro-cognition in patients with skull base meningiomas is worse than in patients with convexity meningiomas[11]. Meningioma patients do not differ from healthy controls with respect to anxiety or depression[12]. In spinal meningiomas, pain, paraparesis and spinal ataxia are the typical presenting ~~signs and~~ symptoms and signs, reflecting spinal cord compression[5].

Pathogenesis and risk factors

Meningiomas are assumed to derive from arachnoid cap cells. The arachnoid mater is the middle part of the meninges whose origin is best described as mesenchymal. Meningiomas exhibit epithelial features such as multiple intercellular gap junctions and expression of the epithelial membrane antigen. They usually occur where meninges are present. However, intraventricular meningioma is an important differential diagnosis for tumors of the lateral ventricles. These tumors are believed to arise from arachnoid cells entrapped in the choroid plexus during organogenesis. Although rare, distant metastases of meningioma to ~~the~~ lung and other sites have been described, not only with anaplastic (WHO grade III) meningiomas. Multiplicity of meningioma is observed and clonality has been

demonstrated in approximately half of the patients with two spatially separated meningioma manifestations, and in all patients with three or more meningioma manifestations[13].
Exposure to ionizing radiation has been firmly linked to a higher risk for meningiomas and radiation-associated meningiomas are more likely to be atypical or malignant and multifocal[14-18]. ~~. Type 2 neurofibromatosis (NF2) is the most common genetic condition associated with an elevated risk for developing meningiomas. Patients with NF2 also may be more likely to develop malignant or multiple meningiomas.~~ Based on the observations of (i) higher incidences in women of reproductive age, (ii) tumor expression of hormone receptors, (iii) an association with breast cancer and (iv) changes in meningioma size during pregnancy, the menstrual cycle and menopause, a number of studies have sought to link endogenous and exogenous hormone exposure to meningioma growth, without significant correlations[3,19].

Diagnostic procedures

Imaging

Cerebral magnetic resonance imaging (MRI) and computed tomography (CT) scans, when used in combination, allow the diagnosis of intracranial meningioma ~~with high probability~~ in most cases[20]. MRI should comprise the sequences T1, T2 spin echo, T2 gradient echo, fluid-attenuated inversion recovery (FLAIR), 3D time-of-flight (TOF) and T1 with gadolinium (see figure 2, main text). When the meningioma is located close to a major dural sinus vein, venous MRI angiography should be included to verify its patency. CT may be valuable in conjunction with MRI and should comprise bone window settings. Typically, meningiomas present as solitary round tumors, with close contact to the dura mater and strong enhancement after contrast injection. The typical signal of meningioma is isointense on T1, iso- or hyperintense on FLAIR and with high and homogenous enhancement following gadolinium injection. On T2, the meningeal arteries can sometimes be seen as lines of low signal radiating from the center of the tumor (typical “sunburst” appearance). Thickening of the dura mater at the perimeter of the tumor (~~so-called~~ *dural tail*) is displayed by T1 with gadolinium[21]. Extra-axial growth can be verified on T2 MRI by CSF interposed between the tumor and the parenchyma[22]. FLAIR and T2 sequences depict edema of the surrounding cerebral parenchyma. CT is valuable for the detection of calcification of varying degrees within the tumor, hyperostosis of adjacent bone and intraosseous tumor growth. Conventional cerebral angiography is no longer used for the diagnosis of meningioma and is restricted as an adjunct to selected cases. If cerebral angiography is performed, it shows a typical tumoral blush in most cases fed by the middle meningeal artery within the aspect of sunburst. Differential diagnoses of meningioma include vestibular schwannoma, if located in the cerebellopontine angle, meningeal metastasis, and hemangiopericytoma, if hypervascularity is seen. Meningiomas may express somatostatin receptor 2 and can be delineated from healthy tissue by positron emission tomography (PET) using peptide ligands such as (68)Ga-Dotatate or (90)Y-Dotatoc ~~as PET tracers~~[23,24].

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Histopathology

The current world health organization (WHO) classification system recognizes 15 different meningioma entities, 9 of which are allotted WHO grade I, 3 WHO grade II and 3 WHO grade III (see ~~Tcompare to t~~able 1, ~~of the~~ main text[25]~~body of the guideline paper)~~ ~~(Table 1)~~. Some of these subtypes are associated with distinct clinical features: For example, secretory meningioma is frequently accompanied by pronounced peritumoral edema, or psammomatous meningioma is predominantly seen in the spinal meninges. Over all, the distinction between the 9 WHO grade I meningioma variants is of limited clinical relevance. On the other hand, grading of meningioma is of major clinical importance, because patients with WHO grade II and grade III meningiomas are considered candidates for postsurgical radiotherapy as discussed below. Grading of meningioma depends on mitotic rate as well as~~,~~ presence of brain invasion or ~~presence of some~~ specific histological features. In the new WHO classification for central nervous system tumors brain invasion became a criteriu~~m~~~~on~~ to assign~~llow~~ a WHO grade II as a single defining feature. Nevertheless, ~~T~~the currently applied parameters for defining the borders between the grades are not entirely satisfactory. While patient cohorts with WHO grade II meningioma generally exhibit shorter intervals to tumor recurrence, there is a considerable number of individual patients with WHO grade I meningiomas ~~WHO grade I~~ with unexpectedly early tumor relapse. Conversely, some patients with WHO grade II meningioma, especially when a complete resection can be achieved, experience a ~~very pro~~long~~ed~~ indolent clinical course even without adjuvant radiotherapy.

Molecular pathology

The current dynamics in the analysis of human tumors with massive parallel sequencing have provided novel insights into molecular mechanisms involved in the formation and progression of meningiomas. Several genes beyond NF2 have been detected as frequently mutated in these tumors - for example KLF4 (exclusively) and TRAF7 (commonly) are ~~always~~ mutated in secretory meningioma[26]. NF2 mutations predominate in meningiomas with some spindle cell morphology encompassing fibroblastic, transitional and psammomatous meningioma. AKT1 exhibits the E17K hotspot mutation in a fraction of meningiomas of basal localization and potentially these tumors have actionable targets using specific inhibitors[27,28]. Another gene with recurrent mutations is SMO[29,30]. These mutations seem to follow a pattern, thus creating molecular subgroups with characteristic combinations of mutations. ~~It is of interest that mutations in these genes are not randomly distributed in meningiomas but form groups with typical combinations of mutations and exclusion of other mutations.~~ It is expected that a future molecularly based classification will ~~be developed and that this classification~~ ha~~ve~~s the potential to direct individualized meningioma-specific therapy (see T~~compare~~ tables ~~23~~ and ~~53~~, ~~of the~~ main text~~body of the guideline)~~ ~~(tables 2 & 4)~~. P~~More relevant, p~~reliminary findings point to TERT mutations, irrespective of WHO grade, being an indicator for more aggressive growth in meningioma[31,32]. ~~Likewise, PIK3CA mutations are associated with higher meningioma grades.~~ Molecular alterations associated with less favorable clinical courses are expected to provide guidance ~~develop as valuable adjuncts to tumor grading~~ for identifying patients at higher risk for

meningioma recurrence or progression and earlier need for targeted intervention. ~~T~~In the future, tumor tissue sampling and storage for future molecular testing should become standard of practice~~will allow for a better understanding of the molecular signatures of the various meningioma types, and for a correlation of those signatures with the risk of tumor recurrence. (compare to table 1 of the main body of the guideline). Additional work to correlate molecular signatures with tumor recurrence is needed to more reliably select and predict which patients will benefit from adjuvant therapy~~.

Therapeutic strategies

Observation and decision making

Meningiomas are a common finding on cranial MRI, and are often discovered incidentally[33]. If a meningioma is diagnosed provisionally by neuroimaging, it must be ascertained if (1) the finding has a clinical correlate, (2) ~~the~~ symptoms or signs, if any, may be relieved by treating the tumor, and if (3) the potential benefits from treatment outweigh the associated risks. If the answer is no to any of these three questions, observation may be the best strategy unless there is diagnostic doubt, necessitating early verification of the diagnosis. Observation is a preferred strategy in many cases of suspected meningioma, especially in small, incidentally discovered tumors. Although class I or II evidence is missing in order to support guidelines for observation rather than therapy, t~~There is no class I or II evidence to support guidelines for observational management of meningiomas, but t~~here are numerous retrospective series and several reviews validating this concept[6] (evidence level III). The most important determinant for symptom development is tumor size at diagnosis. A diameter of 2 cm or less is associated with a higher risk of growth, but very few of these tumors become symptomatic within a period of 5 years. Another important parameter for symptom development is a growth rate of more than 10% per year[6]. A meta-analysis of 22 retrospective studies ~~-~~identified calcification and absence of peri-tumoural signal change, specifically edema, as factors associated with slower meningioma growth. Such tumors may be managed by active surveillance using MRI, and treatment should be offered only if they become symptomatic or show growth.

Due to the different nature of meningiomas and the dissimilarity of meningioma patients, therapy of these tumors needs to be individualized. Patients should be counseled about the finding and given advice accordingly. Many physicians ~~overlook~~ may underestimate ~~oversee~~ the long-term sequelae of brain surgery. V~~In the study of v~~an der Vossen et al. reported ~~it was shown~~ that 40% of the patients operated for a meningioma experienced cognitive or emotional problems after surgery[34]. ~~-~~If a patient refuses observation as a management strategy ~~even after thorough information,~~ treatment may be justified. If one decides to manage a suspected meningioma by observation alone, it has to be agreed who is responsible for patient follow-up. In an ideal setting, this is done by an experienced neurosurgeon or neurooncologist. The patient should receive written information about the need for follow-up, and the potential consequences of not adhering to the follow-up regimen. Annual MRI scans and clinical outpatient consultations are recommended for an initial period assigning the first scan as a reference.

It is uncertain for how long the follow-up of a meningioma should be continued if there is no sign of growth. If a tumor shows significant growth, and in particular if growth leads to new symptoms, treatment is usually indicated. In these cases, surgery is advocated if feasible[35]. In addition or as alternatives, various schedules of radiotherapy, radiosurgery or combination therapies may be treatment options[36]. It is strongly recommended that these patients are discussed in a multidisciplinary panel of neurosurgeons, radiation oncologists and neuro-oncologists. The patient should be informed about the treatment alternatives and the pros and cons of the options should be presented in an unbiased way so as to allow the patient an informed decision about the choice of treatment.

Surgery

Surgery is the treatment of choice for the majority of symptomatic and enlarging meningiomas, serving the dual role of relieving symptoms and mass effect and providing tissue for distinguishing histological type and WHO grade of malignancy (evidence level II, recommendation level B). Surgical risks should be fully discussed with the patients prior to surgery including location-specific risks. There is no evidence that prophylactic antiepileptic drugs (AEDs) reduce the incidence of peri- or post-operative epilepsy. However, certain locations are more prone to seizures e.g. frontal, temporal, and parietal meningiomas have a higher risk than occipital tumors, and convexity and parasagittal/falx meningiomas have a higher risk than tumors of the skull base[37-39].

Careful pre-operative planning reduces the risk of post-operative deficits. Attention to venous anatomy is a key factor in successful surgery, particularly for meningiomas involving the venous sinuses. Whilest it is generally safe to divide the anterior third of the sagittal sinus, inadvertent damage to cortical veins and intra-diploic venous drainage can lead to post-operative venous infarction with devastating consequences. Image guidance is now routinely used to position the craniotomy and allows image fusion of multiple data sets that provide information about critical neurovascular structures. Meningiomas that involve the skull base may result in holes in the frontal, sphenoid and ethmoid air sinuses - these holes must be sealed off to prevent post-operative cerebrospinal fluid leaks. Care should also be taken when resecting meningiomas near to the optic apparatus so as not to disrupt blood supply which could result in visual loss. Intra-operative neurophysiological monitoring, e.g. facial nerve and brainstem-evoked potentials, may help to minimize neurological deficits.

The general principles of meningioma surgery are dividing the tumor from its blood supply and internal debulking followed by peripheral dissection. The aim is gross total resection including involved dura and bone, but this is determined by tumor location and size. If tumor location does not permit complete resection without significant neurological deficit for the patient, maximum safe resection has to be defined as primary surgical goal. If tumor remnants need to be left, these can be monitored with MRI or treated with post-operative conformal or stereotactic fractionated radiotherapy or radiosurgery, depending on location, size and proximity to critical structures, e.g., cavernous sinus.

Extent of resection (EOR) as iis defined by the Simpson Grade (see table 4, main text) (table 3) that relies on the surgeon's assessment at surgery and is an important prognostic factor for risk of tumor

recurrence[40]. Even thoughif the relevanceactuality and prognotstic strength of the Simpson classification has been questionedpre-dates modern neuro-imaging and several authors see a limited value[41], a recent series shows that the the Simpson classificationit still proved to be valuablehas a role forin assessing the risk of recurrence in recent series[40]. Today, the intraoperative assessment of Simpson grade should be confirmed by postoperative MRI that can be performed within 48 h after surgery or after 3 months to avoid artifacts. In case of incomplete resection or suspected WHO grade II or III meningioma, early MRI within 48 hours should be performed to plan further therapy. In modern neurosurgery, the potential benefit of radical surgical resection must be balanced against the risks of complications and causing neurological deficit. In WHO grade I meningioma, defining EOR as either gross total resection ,resection, i.e. no residual solid tumor, or subtotal resection (STR) is an equally good prognostic factor for tumor recurrence[41]. Several clinical research consortia including the European Organization for Research and Treatment of Cancer (EORTC) and the Radiation Therapy Oncology Group (RTOG) have adopted these definitions for use in prospective clinical trials[42]. Regarding spinal meningiomas, the majority of data supports surgical strategies striving for completeness of excision. Recurrence rates of spinal meningiomas after surgical resection have been reported in the range of 1·3 – 14·7%[43-46]. There is consensus that incomplete resection is a risk factor for recurrence but it is unclear whether Simpson grade I resection achieves better long-term outcome than Simpson grade II resection[43,46-48]. Most papers report lower recurrence rates after resection of the involved dura but at the cost of a higher complication rate, particularly for meningiomas located unfavorably or with prominentsevere calcification[45]. Therefore, Simpson grade I resection should be aimed for in all cases of spinal meningioma with a favorable location, but only if this can be achieved without compromising neurological function and if a safe and uncomplicated dural repair is feasible. For patients with ventrally located meningiomas or with calcified dural attachment, excision of the dura should not be the goal – coagulation of the dural attachment is sufficient.

In conclusionany case, the decision for surgery versus observation should balance the benefit of surgery, i.e. tumor removal versus potential also take into account the long-term sequelae of the surgical treatment. Up to 40% of meningioma patients after surgery experience cognitive or emotional problems such as cognitive complains, anxiety and depression[34].

Kommentiert [G1]: Stimmt das Zitat 12? Es hat zu tun mit Anxiety depression…???

Radiotherapy

External beam radiation therapy (RT) has been used extensively in patients with meningioma for the following indications: (i) in tumor locations not amenable to surgery, (ii) in tumors that are not completely resected, (iii) in atypical and malignant tumors and (iv) in recurrent tumors. No randomized or prospectively controlled studies have evaluated the survival and tumor control and survival after conventional RT. Nevertheless, retrospective studies of patients with residual or recurrent WHO grade I meningiomas report a local control rate of 75-90% at 10 years[49-53]. In a series of 82 patients with skull base meningiomas treated with conventional RT, Nutting et al. reported 5-year and 10-year local tumor control rates of 92% and 83%, respectively[52]. In another series of 101 patients treated with 3-dimensional (3D) conformal RT, Mendenhall et al. reported a local control of 95% at 5 years and 92%

at 10 and 15 years, respectively, and cause-specific survival rates of 97% and 92%, respectively[51]. The reported control and survival after subtotal resection and RT are similar to those observed after complete resection, and better than that achieved with incomplete resection alone[54,55] (evidence level III, recommendation level B).

Large skull base meningiomas may present a therapeutic challenge. Also in these tumors, RT has been suggested as an effective treatment. A 5-year tumor control in the range of 90 to 97% has been reported for skull base meningiomas up to 5 cm in greatest dimension[53,56,57]; however, meningiomas larger than 5 cm in size seem to be associated with worse local control[58,59]. There is little evidence that timing of RT is important, as local control and survival rates are similar whether the treatment is given as a part of the primary treatment or at the time of recurrence[51-53,60]. In most series, the administered dose ranged between 50 and 57 Gy delivered in daily fractions of 1.8-2 Gy. The tumor control rates were similar for doses of 50-55 Gy or > 55 Gy[51,53,57,59-64]. Doses below 50 Gy were associated with higher, mostly local recurrence rates[51,60].

There is a significant long-term risk of cognitive impairment after ~~brain tumor radiotherapy~~RT to the brain[65]. In order to spare tumor-surrounding sensitive neurovascular structures, technical advances have enabled administration of fractionated RT by the use of intensity modulated radiation therapy (IMRT) and fractionated stereotactic radiotherapy (FSRT). FSRT has shown to improve symptoms within 1-3 months after treatment[66]. Using FSRT with median doses of 57 Gy, Milker-Zabel et al. reported a 10-year local control of 89% in 317 patients with either skull base or intracranial meningiomas, and similar tumor control rates have been observed in other series of FSRT[59,62,67,68]. Combs et al. evaluated the outcomes of 506 patients with skull base meningiomas who received FSRT (n =376) or IMRT (n=131), reporting a similar local control of 91% at 10 years for patients with WHO grade I meningiomas[67]. Thus, both techniques are probably effective as primary and salvage treatment for meningiomas, with a local control at 5 and 10 years similar to that reported with conformal RT. Particle therapies like proton and carbon ion irradiation allow a high dose deposition on the tumor providing very low doses to the surrounding adjacent tissues via the “Bragg Peak”. Irradiation and re-irradiation of meningioma using protons or carbon ions as stand-alone therapies or in combination with photon therapy have been reported to be well tolerated and to allow dose escalation, particularly in WHO grade II and III meningioma, showing good local control rates[61,69-71]. There is some evidence that dose escalation >60 Gy or even 65 Gy could lead to a better cause specific survival in patients with atypical and malignant meningioma[69]. However, proton therapy remains~~has yet~~ to be evaluated in prospective clinical trials.

The role of RT for WHO grade II meningiomas, specifically its timing, remains unclear. In a series of 83 patients of whom 66% had undergone GTR, Park et al. reported a 5-year tumor control of 59% versus 44% with and without postoperative RT~~, respectively~~[72]. Improved progression-free survival rates after postoperative RT have been observed in comparative retrospective series[73-75]. On the contrary, other studies showed no advantages in terms of progression-free survival for adjuvant RT[76-78]. For WHO grade III meningiomas, postoperative RT using doses of 55-60 Gy in 1.8-2.0 Gy daily

fractions is an established treatment by consensus. There is a trend toward longer survival for patients who had received adjuvant RT after surgery compared to those treated with surgery alone[79,80].

Current clinical trials address the question of dose: In the RTOG 0539 trial, ~~"WHO grade II meningiomas~~ intermediate risk" meningiomas (i.e. recurrent WHO grade I or WHO grade II after GTR) are treated by RT with 54 Gy in 30 fractions after GTR, while “high risk meningioma” (i.e. WHO grade II recurrent disease, WHO grade II after STR and all WHO grade III) receive up to 60 Gy (NCT00895622). The ~~ongoing~~ EORTC 22042-26042 trial evaluate~~d~~s the efficacy of high-dose radiotherapy (RT) in atypical/malignant meningioma (NCT00626730). In this phase II study, ~~In the EORTC 22042-26042 trial,~~ WHO grade II and grade III tumors post GTR are irradiated with 60 Gy in 30 fractions. After STR, 60 Gy plus a 10 Gy boost on the remaining tumor volume are delivered. The ROAM / EORTC 1308 trial (ISRCTN71502099) ~~is currently recruiting patients~~ is a multicenter, phase III, randomized controlled trial that is currently recruiting patients~~,~~ and will answer the question whether early adjuvant RT reduces recurrence compared with active monitoring in patients, who have undergone GTR of newly diagnosed atypical meningioma. ~~,AM, does early adjuvant radiotherapy reduce recurrence compared with active monitoring?with newly diagnosed atypical meningioma (WHO grade II) who have undergone gross total resection (Simpson I-III) and will randomize between early adjuvant radiotherapy (60 Gy in 30 fractions) and observation to determine whether radiotherapy reduces the risk of tumor recurrence~~[81].

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Radiosurgery

In cases that are associated with increased surgical risk, radiosurgery by gamma knife, cyber knife or other types of linear accelerator can be regarded as an effective alternative for radiologically diagnosed meningiomas. The dose used for radiosurgery in meningiomas is highly dependent upon the technique applied, the prescribed isodose, the proximity of neurovascular structures at risk, as well as the size and configuration of the tumor. Generally, a single coverage dose of 14 to 16 Gy is recommended [77]. Besides direct cellular and toxic effects on tumor cells, the impact of a single high dose irradiation on nutritive microvessels seems to be relevant[82]. Radiosurgery may be indicated – even as first therapeutic option - in particular situations like tumor location in the cavernous sinus or the clivus, multiple meningiomas, partially resected tumors, recurrent meningioma, or in cases where comorbidities preclude open surgery. In these situations, radiosurgery can be used as an exclusive therapeutic option based on neuroimaging alone or as part of a combination therapy together with a planned partial surgical resection. A series of 35 retrospective studies showed 5 year progression free survival (PFS) of 86-100 percent after primary radiosurgery[83]. A study analyzing the outcome of 79 patients with cavernous sinus meningiomas treated by radiosurgery alone revealed a tumor control rate of 89.8% at 10 years[84]. A similar excellent clinical outcome and low toxicity have been reported in a few series with the use of multi-session radiosurgery at doses of 18-25 Gy delivered in 2 to 5 daily fractions in patients with meningiomas larger than 2·5-3·0 cm in size and/or situated close to critical structures[85,86]. Although promising, the limited numbers of patients and follow-up time does not allow drawing definitive conclusions on the use of hypofractionated regimens in routine clinical practice as

an alternative to conventionally fractionated RTradiotherapy. Petroclival meningiomas or sphenoid meningiomas are potential candidates for treatment strategies combining surgery and radiosurgery[49,87]. In the latter tumors, combination therapy allows surgical decompression of the optic apparatus and irradiation of tumor remnants in the cavernous sinus. Radiosurgery has also been selected for treatment of recurrent atypical meningiomas. The overall survival of these patients was 87% after 5 years and 75% after 10 years[88]. Multiple meningiomas and intracranial meningiomatosis might be an indication for radiosurgery, if there is no more treatment potential for surgery or fractionated RTradiotherapy[89].

There are no prospective randomized data comparing fractionated RT and radiosurgery. The control rates 5 and 10 years after RT or radiosurgery for WHO grade I meningiomas are very similar. Ten10 year PFS after RT using FSRT or IMRT was reported as 91% whereas 83 to 97% are documented for radiosurgery[67,90]. Radiosurgery allows treatment of a circumscribed volume using a single dose, therefore achieving a high patient comfort. On the other hand, the use of radiosurgery is limited to small and non-infiltrative disease and locations distant from sensitive critical structures such as visual pathways because of the radiosensitivity of late reacting normal tissue to dose per fraction. In these indications, fractionated RT that sometimes can be performed using the same machines is preferred to radiosurgery. In case of infiltrative meningioma growth or WHO grade II or III meningiomas, which have a high recurrence rate, fractionated techniques seem superior[91].

Any decision for RT should take into account the long-term side effects of RTradiation therapy, and these should be discussed with the patient. In the literature, Tthe incidence of treatment toxicity ranges from 3.,4% to 16.,7%. Neurocognitive impairment has been described in 53% of cases[65]. Although blindness due to involvement of the neuro-optic structures into the treatment field hais been reported to occurring in 5% of patients, newer studies show this risk to be significantly lower, probably due to the modern treatment techniques and doses[92,93]. If the pituitary gland receives irradiation, there may be changes in hormonal levels; although hypogonadism is relatively rare (up to 6%), hypopituitarism is reported in up to 50% of cases, and early involvement of the endocrinologist is advisable[92].

Peptide Receptor Radionuclide Therapy (PRRT)

Some meningiomas show prominent expression of somatostatin receptors and peptide receptor radionuclide therapy (PRRT) using radiopeptides targeting somatostatin receptors such as 90Y-DOTATOC ([90Y-DOTA0, Tyr3]-octreotide), 177Lu-DOTATATE ([177Lu-DOTA0,Tyr3]-octreotate) and 111In-Pentreotide has been evaluated in small series or singular cases of somatostatin receptor-positive meningiomas. PRRT was well tolerated and some disease stabilizations and few partial responses were reported. However, the available evidence is anecdotal and well designed studies are needed to evaluate the role of PRRT in meningiomas. In the meantime, PRRT should preferentially be offered in the framework of clinical studies[94-98].

Embolization

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Preoperative embolisation of meningiomas aims ate reducinge blood loss during surgical resection[99-101]. ~~Unlike some hypervascular tumors, such as hemangioblastomas, for which embolisation is almost always carried out prior to surgery,~~ Indications for embolisation of meningiomas vary substantially depending on the neurosurgical team[102]. There is no controlled study that shows better clinical outcomes of surgery if ~~it has been~~ preceded by pre-operative embolisation. Consequently, there is no general indication for embolisation of meningioma; individual indications are assessed on a case by case basis by each team. The principle is to first and foremost occlude the afferent arteries that cannot be reached by the surgeon when accessing the tumor. This is performed by free flow particle injection or coil embolisation within 24 hours of planned surgery. Complications may arise when the neuroradiologist tries to distally guide the embolus into the capillary bed of the tumor. This can result in tumor hemorrhage, erratic embolisation through anastomosis or cranial nerves palsy[103,104]. Four different anatomical scenarios can be discussed: (i) In the very common convexity meningiomas, there is infrequently an indication for preoperative embolisation. If an embolisation is indicated, 100 to 300 µm particles are injected into the middle meningeal artery. These small particles allow a more distal penetration into the tumor bed. This results in a more substantial necrotic effect on the tumor, but their use also entails a higher risk of intra-tumoral hemorrhage[103,105]. A controlled study indicated that preoperative embolisation resulted in a significant reduction of perioperative blood loss[99]. Reported complications are tumor hemorrhage and ischemia due to erratic movement of the emboli. The incidence of complications varies from 0 to 9 %. (ii) Olfactory meningiomas are generally vascularized by ethmoidal arteries. Since these are branches of the ophthalmic artery implicating a risk of jeopardizing vision by embolisation, these tumors should never be embolized. (iii) Meningiomas of the cavernous sinus can be subjected to preoperative embolisation. However, the afferent arteries are small-sized dural arteries emanating from the carotid siphon which, aside from rare cases, are not amenable to selective catherization. Therefore, if an indication for embolisation of a cavernous sinus meningioma is made in very rare cases due to a lack of therapeutic alternatives, the internal carotid artery would needs to be occluded after testing patency of the Circle of Willis. (iv) Petroclival meningiomas can be embolised via the meningeal trunk of the ascending pharyngeal artery. This artery cannot be controlled ~~by the neuro~~surgicallyeon during lateral approaches to the clivus, the petrous bone or the cerebellopontine angle[106].

Pharmacotherapy and experimental therapies

Pharmacotherapy of meningiomas is typically considered in the following main patient populations: (i) patients with recurrent or progressive meningiomas of all tumor grades in whom surgical resection or ~~radiotherapy~~ RT are no longer feasible, and (ii) patients with metastatic meningioma. Principally, systemic therapy appears to be able to inhibit meningioma growth to some extent[107]. A variety of drugs have been studied in meningiomas. However, the interpretation of most of the available studies is limited by several factors, in particular small patient numbers, the retrospective design of most studies, the heterogeneity of patient populations with regard to tumor type and prior therapies, the lack of comparator treatment arms or reliable historical benchmark activity parameters and the lack of standardized response criteria. Thus, pharmacotherapy of meningioma has so far an unclear benefit

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and has to be considered experimental. Overall, inclusion of patients with meningiomas in clinical trials evaluating novel treatment approaches is recommended. Depending on ongoing molecular classification of meningiomas, targeted therapies are evolving (seecompare Ttable 53, of the main textbody of the guideline) (table 4).

WHO grade I meningiomas

Hydroxyurea, temozolomide, irinotecan, interferon-alpha, sandostatin LAR, pasireotide LAR, imatinib, erlotinib and gefitinib have been studied in retrospective and single-arm phase II studies in WHO grade I meningiomas that have failed surgical resection and radiotherapy[108,109]. Mifepristone was studied in a randomized phase III trial but failed to show any advantage over placebo[110]. The PFS-6 rates in these studies ranged from 0% to 67%, while median OS times were only inconsistently reported and ranged from 7 to 13 months[108]. The lack of clear data on the natural course and the uncontrolled character of these studies preclude definite conclusions. Based on the available data, none of the evaluated drugs showed clear signs of clinically relevant activity sufficient to recommend them for standard practive clinical use. Notably tTemozolomide is not active in meningioma[111].

WHO grade II and III meningiomas

Retrospective studies and small prospective studies have evaluated a range of drugs including hydroxyurea, cycophosphamide/adriamycin/vincristine chemotherapy, interferon-alpha, megestrol acetate, medroxy-progesterone acetate, octreotide, sandostatin LAR, pasireotide LAR, imatinib, erlotinib, gefitinib, vatalanib, sunitinib and bavacizumab in patients with WHO grade II and III meningiomas[108]. PFS-6 rates ranged from 0% to 64% and median OS times from 6 to 33 months in patients progressing after surgical resection and radiotherapy[108]. The most promising results have been reported for bevacizumab, vatalanib and sunitinib, all drugs with anti-angiogenic properties[107,108,112-114]. These results need to be confirmed in prospective controlled trials, before clinical use of these compounds in patients with WHO grade II and III meningiomas can be recommended. An ongoing EORTC phase II trial (NCT02234050) explores the efficacy of trabectedin, a tetrahydroisoquinoline that has shown promising activity in recurrent WHO grade II and grade III meningiomas[115].

Surveillance and follow up of meningiomas

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There is only litte no robust data available on the best follow-up schedule for meningiomas. since most retrospective studies do not report on monitoring intervals and since prospective studies published so far had variable follow-up protocols, usually tailored to fit the treatment visits. Therefore, the following recommendations are based more on expert consensus opinion rather than evidence.

An experienced neurosurgeon or neurooncologist should be in charge for the follow up.Follow up should be performed clinically by an experienced neurosurgeon or neurooncologist and. This must be accompanied in special cases by additional specialists, e.g., an ophthalmologist should closely

monitor the visual status in case of a tuberculum sellae meningioma~~s~~ or an audiologist should monitor the hearing level in case of a cerebell~~r~~opontine angle tumor. The ~~re is a considerable variation in~~ follow up intervals ~~possible which~~ should depend not only from resection status, size and location of the tumor, but also age and the general and neurological status of the patient.

~~Our proposed approach on the management of~~For small, asymptomatic meningiomas we suggest ~~is to evaluate the dynamics of the tumor with~~ MRI with contrast medium 6 months after ~~initial~~ diagnosis and then annually, as long as the patient remains asymptomatic. After five years this interval can be doubled. In patients where the identification of ~~a~~ tumor progression has no clinical relevance or consequense, e.g. patients with limited life expectancy due to high age or severe co-morbidities, controls may be omitted~~. if the radiological diagnosis of a benign meningioma seems clear~~.

Monitoring after initial treatment should depend on the extent of resection and grading of the tumor. Even for~~For~~ WHO I meningiomas resected totally, the 10-year recurrence rate ~~in the literature~~ is reported up to~~s vary from 20-~~ 39% and ~~. Studies with long follow-up with MRI show that recurrence i~~thus more common than previously thought. ~~Therefore, it is advisable to perform a baseline MRI within 48 hours or after 3 months, in order to assess the EOR~~The EOR should be controlled with a baseline MRI either within 48 hours after the operation or after 3 months. Thereafter, we ~~propose~~ suggest annual MRI controls ~~until~~ for the first five years ~~post treatment, then every two years~~and then biannually.

If resection is known to be incomplete, EOR should be documented by early postoperative MRI within 48 hours. For WHO grade I tumors after STR, the 10-year progression rates vary between 55 and 100% suggesting a more vigilant long-term follow-up[116,117]. For those cases, MRI at 6 and 12 months is recommended, then annually.

The course of patients with~~natural history of~~ WHO grade II meningiomas might vary within a wide range~~is less clear, since the 2007 WHO criteria changed their definition and thus their identification rates~~. The 5-year recurrence/progression rates are reported ~~may be as high~~ as 30% and 40% after GTR and STR, respectively[73,76].To monitor these tumors ~~In these tumors~~, we suggest an early postoperative MRI within 48 hours as a basis for further observation. Follow~~-~~up MRI should be done every 6 months for 5 years, then annually.

WHO grade III meningiomas are aggressive tumors with very poor local control, even after multimodal treatment. In the recent studies utilizing the WHO 2007 grading scheme, the 5-year-PFS ranged from 12 to 57%, even after resection and RT~~radiotherapy~~. ~~Therefore,~~For these tumors ~~have to be followed up~~ very close follow-up is ~~to be~~ recommended~~ly~~[118]. After the initial, early post-treatment MRI, cranial imaging should be routinely done every 6 months, in rapidly growing cases every 3 months.

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Appendix:

Epidemiology and clinical presentation

Meningiomas have the highest incidence rate among all intracranial and intraspinal tumors. In European countries the annual incidence rate of meningiomas is 4.-2 per 100·000 individuals[1,2]. The median age at diagnosis is 65 years and incidence increases with age[3]. The majority of intracranial meningiomas are found in the supratentorial compartment, most commonly at the cerebral convexity, along the dural venous sinuses, along the falx or intraventricularly. Skull base meningiomas grow at the sphenoid wing, olfactory groove, clinoid process or petroclival regions. Additional sites include the cerebellopontine angle, the foramen magnum or – less commonly – the optic nerve sheath. Moreover, meningiomas represent 25-45% of intradural spinal tumors[4]. Eighty percent of spinal meningiomas are located in the thoracic spine[5]. Many meningiomas are asymptomatic and diagnosed incidentally. There is no clearly defined critical size for the development of symptoms in general, however, meningiomas that do not exceed 2.5 cm in diameter rarely cause symptoms within 5 years of being discovered[6]. An exception can be smaller meningiomas, growing close to critical structures (such as the optic nerve) or meningiomas with disproportionally large edema or rate of growth. The most common symptoms are epilepsy, or headache for weeks to months, or location-specific symptoms or signs such as unilateral weakness, visual field loss, changes in personality or speech problems. Meningioma patients exhibit diminished neurocognitive function as compared with healthy controls except for intelligence and visuoconstructive skills[7-11]. Neurocognitive functions in patients with meningiomas in the dominant hemisphere (usually left-side) are more compromised than in patients with meningiomas in the non-dominant hemisphere (usually right-side). Furthermore, neuro-cognition in patients with skull base meningiomas is worse than in patients with convexity meningiomas[11]. Meningioma patients do not differ from healthy controls with respect to anxiety or depression[12]. In spinal meningiomas, pain, paraparesis and spinal ataxia are the typical presenting symptoms and signs, reflecting spinal cord compression[5].

Pathogenesis and risk factors

Meningiomas are assumed to derive from arachnoid cap cells. The arachnoid mater is the middle part of the meninges whose origin is best described as mesenchymal. Meningiomas exhibit epithelial features such as multiple intercellular gap junctions and expression of the epithelial membrane antigen. They usually occur where meninges are present. However, intraventricular meningioma is an important differential diagnosis for tumors of the lateral ventricles. These tumors are believed to arise from arachnoid cells entrapped in the choroid plexus during organogenesis. Although rare, distant metastases of meningioma to lung and other sites have been described, not only with anaplastic (WHO grade III) meningiomas. Multiplicity of meningioma is observed and clonality has been demonstrated in approximately half of the patients with two spatially separated meningioma manifestations, and in all patients with three or more meningioma manifestations[13].

Exposure to ionizing radiation has been firmly linked to a higher risk for meningiomas and radiation-associated meningiomas are more likely to be atypical or malignant and multifocal[14-18]. Based on the observations of (i) higher incidences in women of reproductive age, (ii) tumor expression of hormone receptors, (iii) an association with breast cancer and (iv) changes in meningioma size during pregnancy, the menstrual cycle and menopause, a number of studies have sought to link endogenous and exogenous hormone exposure to meningioma growth, without significant correlations[3,19].

Diagnostic procedures

Imaging

Cerebral magnetic resonance imaging (MRI) and computed tomography (CT) scans, when used in combination, allow the diagnosis of intracranial meningiomain most cases[20]. MRI should comprise the sequences T1, T2 spin echo, T2 gradient echo, fluid-attenuated inversion recovery (FLAIR), 3D time-of-flight (TOF) and T1 with gadolinium (see figure 2, main text). When the meningioma is located close to a major dural sinus vein, venous MRI angiography should be included to verify its patency. CT may be valuable in conjunction with MRI and should comprise bone window settings. Typically, meningiomas present as solitary round tumors, with close contact to the dura mater and strong enhancement after contrast injection. The typical signal of meningioma is isointense on T1, iso- or hyperintense on FLAIR and with high and homogenous enhancement following gadolinium injection. On T2, the meningeal arteries can sometimes be seen as lines of low signal radiating from the center of the tumor (typical “sunburst” appearance). Thickening of the dura mater at the perimeter of the tumor (*dural tail*) is displayed by T1 with gadolinium[21]. Extra-axial growth can be verified on T2 MRI by CSF interposed between the tumor and the parenchyma[22]. FLAIR and T2 sequences depict edema of the surrounding cerebral parenchyma. CT is valuable for the detection of calcification of varying degrees within the tumor, hyperostosis of adjacent bone and intraosseous tumor growth. Conventional cerebral angiography is no longer used for the diagnosis of meningioma and is restricted as an adjunct to selected cases. If cerebral angiography is performed, it shows a typical tumoral blush in most cases fed by the middle meningeal artery within the aspect of sunburst. Differential diagnoses of meningioma include vestibular schwannoma, if located in the cerebellopontine angle, meningeal metastasis, and hemangiopericytoma, if hypervascularity is seen. Meningiomas may express somatostatin receptor 2 and can be delineated from healthy tissue by positron emission tomography (PET) using peptide ligands tracers such as (68)Ga-Dotatate or (90)Y-Dotatoc[23,24].

Histopathology

The current world health organization (WHO) classification system recognizes 15 different meningioma entities, 9 of which are allotted WHO grade I, 3 WHO grade II and 3 WHO grade III (see Table 1, main text[25]. Some of these subtypes are associated with distinct clinical features: For example, secretory meningioma is frequently accompanied by pronounced peritumoral edema, or

psammomatous meningioma is predominantly seen in the spinal meninges. Over all, the distinction between the 9 WHO grade I meningioma variants is of limited clinical relevance. On the other hand, grading of meningioma is of major clinical importance, because patients with WHO grade II and grade III meningiomas are considered candidates for postsurgical radiotherapy as discussed below. Grading of meningioma depends on mitotic rate as well as presence of brain invasion or specific histological features. In the new WHO classification for central nervous system tumors brain invasion became a criterium to assign a WHO grade II as a single defining feature. Nevertheless, the currently applied parameters for defining the borders between the grades are not entirely satisfactory. While patient cohorts with WHO grade II meningioma generally exhibit shorter intervals to tumor recurrence, there is a considerable number of individual patients with WHO grade I meningiomas with unexpectedly early tumor relapse. Conversely, some patients with WHO grade II meningioma, especially when a complete resection can be achieved, experience a long indolent clinical course even without adjuvant radiotherapy.

Molecular pathology

The current dynamics in the analysis of human tumors with massive parallel sequencing have provided novel insights into molecular mechanisms involved in the formation and progression of meningiomas. Several genes beyond NF2 have been detected as frequently mutated in these tumors - for example KLF4 (exclusively) and TRAF7 (commonly) are mutated in secretory meningioma[26]. NF2 mutations predominate in meningiomas with some spindle cell morphology encompassing fibroblastic, transitional and psammomatous meningioma. AKT1 exhibits the E17K hotspot mutation in a fraction of meningiomas of basal localization and potentially these tumors have actionable targets using specific inhibitors[27,28]. Another gene with recurrent mutations is SMO[29,30]. These mutations seem to follow a pattern, thus creating molecular subgroups with characteristic combinations of mutations. It is expected that a future molecularly based classification will have the potential to direct individualized meningioma-specific therapy (see tTables 2 and 3, main text). Preliminary findings point to TERT mutations, irrespective of WHO grade, being an indicator for more aggressive growth in meningioma[31,32]. Molecular alterations associated with less favorable clinical courses are expected to provide guidance for identifying patients at higher risk for meningioma recurrence or progression and earlier need for targeted intervention. Tumor tissue sampling and storage for future molecular testing should become standard of practice. .

Therapeutic strategies

Observation and decision making

Meningiomas are a common finding on cranial MRI, and are often discovered incidentally[33]. If a meningioma is diagnosed provisionally by neuroimaging, it must be ascertained if (1) the finding has a clinical correlate, (2) symptoms or signs, if any, may be relieved by treating the tumor, and if (3) the potential benefits from treatment outweigh the associated risks. If the answer is no to any of these

three questions, observation may be the best strategy unless there is diagnostic doubt, necessitating early verification of the diagnosis. Observation is a preferred strategy in many cases of suspected meningioma, especially in small, incidentally discovered tumors. Although class I or II evidence is missing in order to support guidelines for observation rather than therapy, there are numerous retrospective series and several reviews validating this concept[6] (evidence level III). The most important determinant for symptom development is tumor size at diagnosis. A diameter of 2 cm or less is associated with a higher risk of growth, but very few of these tumors become symptomatic within a period of 5 years. Another important parameter for symptom development is a growth rate of more than 10% per year[6]. A meta-analysis of 22 retrospective studies identified calcification and absence of peri-tumoural signal change, specifically edema, as factors associated with slower meningioma growth. Such tumors may be managed by active surveillance using MRI, and treatment should be offered only if they become symptomatic or show growth.

Due to the different nature of meningiomas and the dissimilarity of meningioma patients, therapy of these tumors needs to be individualized. Patients should be counseled about the finding and given advice accordingly. Many physicians may underestimate the long-term sequelae of brain surgery. Van der Vossen et al. reported that 40% of the patients operated for a meningioma experienced cognitive or emotional problems after surgery[34]. If a patient refuses observation as a management strategy treatment may be justified. If one decides to manage a suspected meningioma by observation alone, it has to be agreed who is responsible for patient follow-up. In an ideal setting, this is done by an experienced neurosurgeon or neurooncologist. The patient should receive written information about the need for follow-up, and the potential consequences of not adhering to the follow-up regimen. Annual MRI scans and clinical outpatient consultations are recommended for an initial period assigning the first scan as a reference.
It is uncertain for how long the follow-up of a meningioma should be continued if there is no sign of growth. If a tumor shows significant growth, and in particular if growth leads to new symptoms, treatment is usually indicated. In these cases, surgery is advocated if feasible[35]. In addition or as alternatives, various schedules of radiotherapy, radiosurgery or combination therapies may be treatment options[36]. It is strongly recommended that these patients are discussed in a multidisciplinary panel of neurosurgeons, radiation oncologists and neuro-oncologists. The patient should be informed about the treatment alternatives and the pros and cons of the options should be presented in an unbiased way so as to allow the patient an informed decision about the choice of treatment.

Surgery

Surgery is the treatment of choice for the majority of symptomatic and enlarging meningiomas, serving the dual role of relieving symptoms and mass effect and providing tissue for distinguishing histological type and WHO grade of malignancy (evidence level II, recommendation level B). Surgical risks should be fully discussed with the patients prior to surgery including location-specific risks. There is no evidence that prophylactic antiepileptic drugs (AEDs) reduce the incidence of peri- or post-operative epilepsy. However, certain locations are more prone to seizures e.g. frontal, temporal, and parietal

meningiomas have a higher risk than occipital tumors, and convexity and parasagittal/falx meningiomas have a higher risk than tumors of the skull base[37-39].

Careful pre-operative planning reduces the risk of post-operative deficits. Attention to venous anatomy is a key factor in successful surgery, particularly for meningiomas involving the venous sinuses. While it is generally safe to divide the anterior third of the sagittal sinus, inadvertent damage to cortical veins and intra-diploic venous drainage can lead to post-operative venous infarction with devastating consequences. Image guidance is now routinely used to position the craniotomy and allows image fusion of multiple data sets that provide information about critical neurovascular structures. Meningiomas that involve the skull base may result in holes in the frontal, sphenoid and ethmoid air sinuses - these holes must be sealed off to prevent post-operative cerebrospinal fluid leaks. Care should also be taken when resecting meningiomas near to the optic apparatus so as not to disrupt blood supply which could result in visual loss. Intra-operative neurophysiological monitoring, e.g. facial nerve and brainstem-evoked potentials, may help to minimize neurological deficits.

The general principles of meningioma surgery are dividing the tumor from its blood supply and internal debulking followed by peripheral dissection. The aim is gross total resection including involved dura and bone, but this is determined by tumor location and size. If tumor location does not permit complete resection without significant neurological deficit, maximum safe resection has to be defined as primary surgical goal. If tumor remnants need to be left, these can be monitored with MRI or treated with post-operative conformal or stereotactic fractionated radiotherapy or radiosurgery, depending on location, size and proximity to critical structures, e.g., cavernous sinus.

Extent of resection (EOR) as ~~i~~defined by the Simpson Grade (see table 4, main text) is an important prognostic factor for risk of tumor recurrence[40]. Even though the relevance and prognostic strength of the Simpson classification has been questioned[41], a recent series shows that it still has a role in assessing the risk of recurrence [40]. Today, the intraoperative assessment of Simpson grade should be confirmed by postoperative MRI that can be performed within 48 h after surgery or after 3 months to avoid artifacts. In case of incomplete resection or suspected WHO grade II or III meningioma, early MRI within 48 hours should be performed to plan further therapy. In modern neurosurgery, the potential benefit of radical surgical resection must be balanced against the risks of complications and causing neurological deficit. In WHO grade I meningioma, defining EOR as either gross total resection, i.e. no residual solid tumor, or subtotal resection (STR) is an equally good prognostic factor for tumor recurrence[41]. Several clinical research consortia including the European Organization for Research and Treatment of Cancer (EORTC) and the Radiation Therapy Oncology Group (RTOG) have adopted these definitions for use in prospective clinical trials[42].
Regarding spinal meningiomas, the majority of data supports surgical strategies striving for completeness of excision. Recurrence rates of spinal meningiomas after surgical resection have been reported in the range of 1.-3 – 14.-7%[43-46]. There is consensus that incomplete resection is a risk factor for recurrence but it is unclear whether Simpson grade I resection achieves better long-term outcome than Simpson grade II resection[43,46-48]. Most papers report lower recurrence rates after

resection of the involved dura but at the cost of a higher complication rate, particularly for meningiomas located unfavorably or with prominent calcification[45]. Therefore, Simpson grade I resection should be aimed for in all cases of spinal meningioma with a favorable location, but only if this can be achieved without compromising neurological function and if a safe and uncomplicated dural repair is feasible. For patients with ventrally located meningiomas or with calcified dural attachment, excision of the dura should not be the goal – coagulation of the dural attachment is sufficient.
In conclusion, the decision for surgery versus observation should balance the benefit of surgery, i.e. tumor removal versus potential long-term sequelae of the surgical treatment[34].

Radiotherapy

External beam radiation therapy (RT) has been used extensively in patients with meningioma for the following indications: (i) in tumor locations not amenable to surgery, (ii) in tumors that are not completely resected, (iii) in atypical and malignant tumors and (iv) in recurrent tumors. No randomized or prospectively controlled studies have evaluated tumor control and survival after conventional RT. Nevertheless, retrospective studies of patients with residual or recurrent WHO grade I meningiomas report a local control rate of 75-90% at 10 years[49-53]. In a series of 82 patients with skull base meningiomas treated with conventional RT, Nutting et al. reported 5-year and 10-year local tumor control rates of 92% and 83%, respectively[52]. In another series of 101 patients treated with 3-dimensional (3D) conformal RT, Mendenhall et al. reported local control of 95% at 5 years and 92% at 10 and 15 years, respectively, and cause-specific survival rates of 97% and 92%, respectively[51]. The reported control and survival after subtotal resection and RT are similar to those observed after complete resection, and better than that achieved with incomplete resection alone[54,55] (evidence level III, recommendation level B).

Large skull base meningiomas may present a therapeutic challenge. Also in these tumors, RT has been suggested as an effective treatment. A 5-year tumor control in the range of 90 to 97% has been reported for skull base meningiomas up to 5 cm in greatest dimension[53,56,57]; however, meningiomas larger than 5 cm in size seem to be associated with worse local control[58,59]. There is little evidence that timing of RT is important, as local control and survival rates are similar whether the treatment is given as a part of the primary treatment or at the time of recurrence[51-53,60]. In most series, the administered dose ranged between 50 and 57 Gy delivered in daily fractions of 1.8-2 Gy. The tumor control rates were similar for doses of 50-55 Gy or > 55 Gy[51,53,57,59-64]. Doses below 50 Gy were associated with higher, mostly local recurrence rates[51,60].

There is a significant long-term risk of cognitive impairment after RT to the brain[65]. In order to spare tumor-surrounding sensitive neurovascular structures, technical advances have enabled administration of fractionated RT by the use of intensity modulated radiation therapy (IMRT) and fractionated stereotactic radiotherapy (FSRT). FSRT has shown to improve symptoms within 1-3 months after treatment[66]. Using FSRT with median doses of 57 Gy, Milker-Zabel et al. reported a 10-

year local control of 89% in 317 patients with either skull base or intracranial meningiomas, and similar tumor control rates have been observed in other series of FSRT[59,62,67,68]. Combs et al. evaluated the outcomes of 506 patients with skull base meningiomas who received FSRT (n =376) or IMRT (n=131), reporting a similar local control of 91% at 10 years for patients with WHO grade I meningiomas[67]. Thus, both techniques are probably effective as primary and salvage treatment for meningiomas, with a local control at 5 and 10 years similar to that reported with conformal RT. Particle therapies like proton and carbon ion irradiation allow a high dose deposition on the tumor providing very low doses to the surrounding adjacent tissues via the "Bragg Peak". Irradiation and re-irradiation of meningioma using protons or carbon ions as stand-alone therapies or in combination with photon therapy have been reported to be well tolerated and to allow dose escalation, particularly in WHO grade II and III meningioma, showing good local control rates[61,69-71]. There is some evidence that dose escalation >60 Gy or even 65 Gy could lead to a better cause specific survival in patients with atypical and malignant meningioma[69]. However, proton therapy remains to be evaluated in prospective clinical trials.

The role of RT for WHO grade II meningiomas, specifically its timing, remains unclear. In a series of 83 patients of whom 66% had undergone GTR, Park et al. reported a 5-year tumor control of 59% versus 44% with and without postoperative RT[72]. Improved progression-free survival rates after postoperative RT have been observed in comparative retrospective series[73-75]. On the contrary, other studies showed no advantages in terms of progression-free survival for adjuvant RT[76-78]. For WHO grade III meningiomas, postoperative RT using doses of 55-60 Gy in 1.8-2.0 Gy daily fractions is an established treatment by consensus. There is a trend toward longer survival for patients who had received adjuvant RT after surgery compared to those treated with surgery alone[79,80].

Current clinical trials address the question of dose: In the RTOG 0539 trial, "intermediate risk" meningiomas (i.e. recurrent WHO grade I or WHO grade II after GTR) are treated by RT with 54 Gy in 30 fractions after GTR, while "high risk meningioma" (i.e. WHO grade II recurrent disease, WHO grade II after STR and all WHO grade III) receive up to 60 Gy (NCT00895622). The EORTC 22042-26042 trial evaluated the efficacy of high-dose radiotherapy (RT) in atypical/malignant meningioma (NCT00626730). In this phase II study, WHO grade II and grade III tumors post GTR are irradiated with 60 Gy in 30 fractions. After STR, 60 Gy plus a 10 Gy boost on the remaining tumor volume are delivered. The ROAM / EORTC 1308 trial (ISRCTN71502099) is a multicenter, phase III, randomized controlled trial that is currently recruiting patients and will answer the question whether early adjuvant RT reduces recurrence compared with active monitoring in patients, who have undergone GTR of newly diagnosed atypical meningioma. ?[81].

Radiosurgery

In cases that are associated with increased surgical risk, radiosurgery by gamma knife, cyber knife or other types of linear accelerator can be regarded as an effective alternative for radiologically diagnosed meningiomas. The dose used for radiosurgery in meningiomas is highly dependent upon the technique applied, the prescribed isodose, the proximity of neurovascular structures at risk, as well as the size and configuration of the tumor. Generally, a single coverage dose of 14 to 16 Gy is

recommended[77]. Besides direct cellular and toxic effects on tumor cells, the impact of a single high dose irradiation on nutritive microvessels seems to be relevant[82]. Radiosurgery may be indicated – even as first therapeutic option - in particular situations like tumor location in the cavernous sinus or the clivus, multiple meningiomas, partially resected tumors, recurrent meningioma, or in cases where comorbidities preclude open surgery. In these situations, radiosurgery can be used as an exclusive therapeutic option based on neuroimaging alone or as part of a combination therapy together with a planned partial surgical resection. A series of 35 retrospective studies showed 5 year progression free survival (PFS) of 86-100 percent after primary radiosurgery[83]. A study analyzing the outcome of 79 patients with cavernous sinus meningiomas treated by radiosurgery alone revealed a tumor control rate of 89.8% at 10 years[84]. A similar excellent clinical outcome and low toxicity have been reported in a few series with the use of multi-session radiosurgery at doses of 18-25 Gy delivered in 2 to 5 daily fractions in patients with meningiomas larger than 2.-5-3.-0 cm in size and/or situated close to critical structures[85,86]. Although promising, the limited numbers of patients and follow-up time does not allow drawing definitive conclusions on the use of hypofractionated regimens in routine clinical practice as an alternative to conventionally fractionated RT. Petroclival meningiomas or sphenoid meningiomas are potential candidates for treatment strategies combining surgery and radiosurgery[49,87]. In the latter tumors, combination therapy allows surgical decompression of the optic apparatus and irradiation of tumor remnants in the cavernous sinus. Radiosurgery has also been selected for treatment of recurrent atypical meningiomas. The overall survival of these patients was 87% after 5 years and 75% after 10 years[88]. Multiple meningiomas and intracranial meningiomatosis might be an indication for radiosurgery, if there is no more treatment potential for surgery or fractionated RT[89].

There are no prospective randomized data comparing fractionated RT and radiosurgery. The control rates 5 and 10 years after RT or radiosurgery for WHO grade I meningiomas are very similar. Ten year PFS after RT using FSRT or IMRT was reported as 91% whereas 83 to 97% are documented for radiosurgery[67,90]. Radiosurgery allows treatment of a circumscribed volume using a single dose, therefore achieving a high patient comfort. On the other hand, the use of radiosurgery is limited to small and non-infiltrative disease and locations distant from sensitive critical structures such as visual pathways because of the radiosensitivity of late reacting normal tissue to dose per fraction. In these indications, fractionated RT that sometimes can be performed using the same machines is preferred to radiosurgery. In case of infiltrative meningioma growth or WHO grade II or III meningiomas, which have a high recurrence rate, fractionated techniques seem superior[91].

Any decision for RT should take into account the long-term side effects of RT, and these should be discussed with the patient. The incidence of treatment toxicity ranges from 3.4% to 16.7%. Neurocognitive impairment has been described in 53% of cases[65] Although blindness due to involvement of the neuro-optic structures into the treatment field has been reported to occur in 5% of patients, newer studies show this risk to be significantly lower, probably due to the modern treatment techniques and doses[92,93]. If the pituitary gland receives irradiation, there may be changes in hormonal levels; although hypogonadism is relatively rare (up to 6%), hypopituitarism is reported in up to 50% of cases, and early involvement of the endocrinologist is advisable[92].

Kommentiert [RG1]: Reference Douw fehlt immer noch!!!

Peptide Receptor Radionuclide Therapy (PRRT)

Some meningiomas show prominent expression of somatostatin receptors and peptide receptor radionuclide therapy (PRRT) using radiopeptides targeting somatostatin receptors such as 90Y-DOTATOC ([90Y-DOTA0, Tyr3]-octreotide), 177Lu-DOTATATE ([177Lu-DOTA0,Tyr3]-octreotate) and 111In-Pentreotide has been evaluated in small series or singular cases of somatostatin receptor-positive meningiomas. PRRT was well tolerated and some disease stabilizations and few partial responses were reported. However, the available evidence is anecdotal and well designed studies are needed to evaluate the role of PRRT in meningiomas. In the meantime, PRRT should preferentially be offered in the framework of clinical studies[94-98].

Embolization

Preoperative embolisation of meningiomas aims at reducing blood loss during surgical resection[99-101].Indications for embolisation of meningiomas vary substantially depending on the neurosurgical team[102]. There is no controlled study that shows better clinical outcomes of surgery if preceded by pre-operative embolisation. Consequently, there is no general indication for embolisation of meningioma; individual indications are assessed on a case by case basis by each team. The principle is to first and foremost occlude the afferent arteries that cannot be reached by the surgeon when accessing the tumor. This is performed by free flow particle injection or coil embolisation within 24 hours of planned surgery. Complications may arise when the neuroradiologist tries to distally guide the embolus into the capillary bed of the tumor. This can result in tumor hemorrhage, erratic embolisation through anastomosis or cranial nerves palsy[103,104]. Four different anatomical scenarios can be discussed: (i) In the very common convexity meningiomas, there is infrequently an indication for preoperative embolisation. If an embolisation is indicated, 100 to 300 µm particles are injected into the middle meningeal artery. These small particles allow a more distal penetration into the tumor bed. This results in a more substantial necrotic effect on the tumor, but their use also entails a higher risk of intra-tumoral hemorrhage[103,105]. A controlled study indicated that preoperative embolisation resulted in a significant reduction of perioperative blood loss[99]. Reported complications are tumor hemorrhage and ischemia due to erratic movement of the emboli. The incidence of complications varies from 0 to 9 %. (ii) Olfactory meningiomas are generally vascularized by ethmoidal arteries. Since these are branches of the ophthalmic artery implicating a risk of jeopardizing vision by embolisation, these tumors should never be embolized. (iii) Meningiomas of the cavernous sinus can be subjected to preoperative embolisation. However, the afferent arteries are small-sized dural arteries emanating from the carotid siphon which, aside from rare cases, are not amenable to selective catherization. Therefore, if an indication for embolisation of a cavernous sinus meningioma is made in very rare cases due to a lack of therapeutic alternatives, the internal carotid artery would need to be occluded after testing patency of the Circle of Willis. (iv) Petroclival meningiomas can be embolised via the meningeal trunk of the ascending pharyngeal artery. This artery cannot be controlled surgically during lateral approaches to the clivus, the petrous bone or the cerebellopontine angle[106].

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Pharmacotherapy and experimental therapies

Pharmacotherapy of meningiomas is typically considered in the following main patient populations: (i) patients with recurrent or progressive meningiomas of all tumor grades in whom surgical resection or RT are no longer feasible, and (ii) patients with metastatic meningioma. Principally, systemic therapy appears to be able to inhibit meningioma growth to some extent[107]. A variety of drugs have been studied in meningiomas. However, the interpretation of most of the available studies is limited by several factors, in particular small patient numbers, the retrospective design of most studies, the heterogeneity of patient populations with regard to tumor type and prior therapies, the lack of comparator treatment arms or reliable historical benchmark activity parameters and the lack of standardized response criteria. Thus, pharmacotherapy of meningioma has so far an unclear benefit and has to be considered experimental. Overall, inclusion of patients with meningiomas in clinical trials evaluating novel treatment approaches is recommended. Depending on ongoing molecular classification of meningiomas, targeted therapies are evolving (see Table 3, main text).

WHO grade I meningiomas

Hydroxyurea, temozolomide, irinotecan, interferon-alpha, sandostatin LAR, pasireotide LAR, imatinib, erlotinib and gefitinib have been studied in retrospective and single-arm phase II studies in WHO grade I meningiomas that have failed surgical resection and radiotherapy[108,109]. Mifepristone was studied in a randomized phase III trial but failed to show an advantage over placebo[110]. The PFS-6 rates in these studies ranged from 0% to 67%, while median OS times were only inconsistently reported and ranged from 7 to 13 months[108]. The lack of clear data on the natural course and the uncontrolled character of these studies preclude definite conclusions. Based on the available data, none of the evaluated drugs showed clear signs of clinically relevant activity sufficient to recommend them for standard practive clinical use. Notably, temozolomide is not active in meningioma[111].

WHO grade II and III meningiomas

Retrospective studies and small prospective studies have evaluated a range of drugs including hydroxyurea, cycophosphamide/adriamycin/vincristine chemotherapy, interferon-alpha, megestrol acetate, medroxy-progesterone acetate, octreotide, sandostatin LAR, pasireotide LAR, imatinib, erlotinib, gefitinib, vatalanib, sunitinib and bavacizumab in patients with WHO grade II and III meningiomas[108]. PFS-6 rates ranged from 0% to 64% and median OS times from 6 to 33 months in patients progressing after surgical resection and radiotherapy[108]. The most promising results have been reported for bevacizumab, vatalanib and sunitinib, all drugs with anti-angiogenic properties[107,108,112-114]. These results need to be confirmed in prospective controlled trials, before clinical use of these compounds in patients with WHO grade II and III meningiomas can be recommended. An ongoing EORTC phase II trial (NCT02234050) explores the efficacy of trabectedin, a tetrahydroisoquinoline that has shown promising activity in recurrent WHO grade II and grade III meningiomas[115].

Surveillance and follow up of meningiomas

There is only litte data available on the best follow-up schedule for meningiomasTherefore, the following recommendations are based more on expert consensus opinion rather than evidence.

An experienced neurosurgeon or neurooncologist should be in charge for the follow-up. This must be accompanied in special cases by additional specialists, e.g., an ophthalmologist should closely monitor the visual status in case of a tuberculum sellae meningioma or an audiologist should monitor the hearing level in case of a cerebellopontine angle tumor. The follow-up intervals should depend not only from resection status, size and location of the tumor, but also age and the general and neurological status of the patient.

For small, asymptomatic meningiomas we suggest MRI with contrast medium 6 months after diagnosis and then annually, as long as the patient remains asymptomatic. After five years this interval can be doubled. In patients where the identification of tumor progression has no clinical relevance or consequense, e.g. patients with limited life expectancy due to high age or severe co-morbidities, controls may be omitted.

Monitoring after initial treatment should depend on the extent of resection and grading of the tumor. Even for WHO I meningiomas resected totally, the 10-year recurrence rate is reported up to 39% and thus more common than previously thought. The EOR should be controlled with a baseline MRI either within 48 hours after the operation or after 3 months. Thereafter, we suggest annual MRI controls for the first five years and then biannually.
If resection is known to be incomplete, EOR should be documented by early postoperative MRI within 48 hours. For WHO grade I tumors after STR, the 10-year progression rates vary between 55 and 100% suggesting a more vigilant long-term follow-up[116,117]. For those cases, MRI at 6 and 12 months is recommended, then annually.
The course of patients with WHO grade II meningiomas might vary within a wide range. The 5-year recurrence/progression rates are reported as 30% and 40% after GTR and STR, respectively[73,76]. To monitor these tumors, we suggest an early postoperative MRI within 48 hours as a basis for further observation. Follow-up MRI should be done every 6 months for 5 years, then annually.
WHO grade III meningiomas are aggressive tumors with very poor local control, even after multimodal treatment. In the recent studies utilizing the WHO 2007 grading scheme, the 5-year-PFS ranged from 12 to 57%, even after resection and RT. For these tumors very close follow-up is recommended[118]. After the initial, early post-treatment MRI, cranial imaging should be routinely done every 6 months, in rapidly growing cases every 3 months.

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